ABSTRACT

Vismodegib, a potent inhibitor of the hedgehog pathway, is an effective treatment for advanced basal cell carcinoma. More recently, it has become recognized that other oral and topical medications exist that also inhibit this pathway. Multifocal inhibition has been shown to work more efficaciously than a single pathway inhibition when treating melanocytic tumors. The authors report the successful treatment of a patient with advanced basal cell carcinoma using the combination of vismodegib, itraconazole, and imiquimod, each of which inhibits a different part of the hedgehog pathway.

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CASE REPORT

Triple Hedgehog Pathway Inhibition for Basal Cell Carcinoma

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A 71-year-old man with a history of nonmelanoma skin cancer presented with a nonhealing plaque around his right lower eyelid and medial canthus measuring 3.2x1.8cm (Figure 1A). The tumor had been present for several years, but recently became symptomatic, causing intermittent irritation of the eye and occasional bleeding. Clinically, the tumor appeared to surround the lower lacrimal canaliculus and involve the caruncle. A biopsy showed invasive basal cell carcinoma (BCC) with an aggressive growth pattern. The patient refused surgery because he is the only caregiver for his wife who has severe dementia. In addition, his right eye is his only functioning eye; the left eye is blind.

The patient was treated with a combination of vismodegib 150mg daily and itraconazole 100mg daily for four months. Side effects included muscle cramps, dysgeusia, and mild hair thinning. Two months into this therapy, topical imiquimod 5% cream daily to the affected area was added. After two weeks, he developed severe crusting of the lower eyelid and right cheek, but did not develop a reaction in the medial canthus (Figure 1B). At this point, and upon the authors' advice, the patient discontinued the imiquimod.

Clinically, there was no sign of tumor at the involved site after four months (Figure 1C). Punch biopsies 4mm in size taken from the involved areas of the medial canthus and lower eyelid were negative for BCC. At this point, the patient was directed to discontinue the vismodegib and itraconazole therapy. He received three monthly follow-ups and there was no clinical reappearance of the tumor at 18 months to date.

DISCUSSION

Hedgehog pathway upregulation has been found in almost all cases of BCC.[1] From the authors' experience, combination blockade targeting different points in the hedgehog (Hh)

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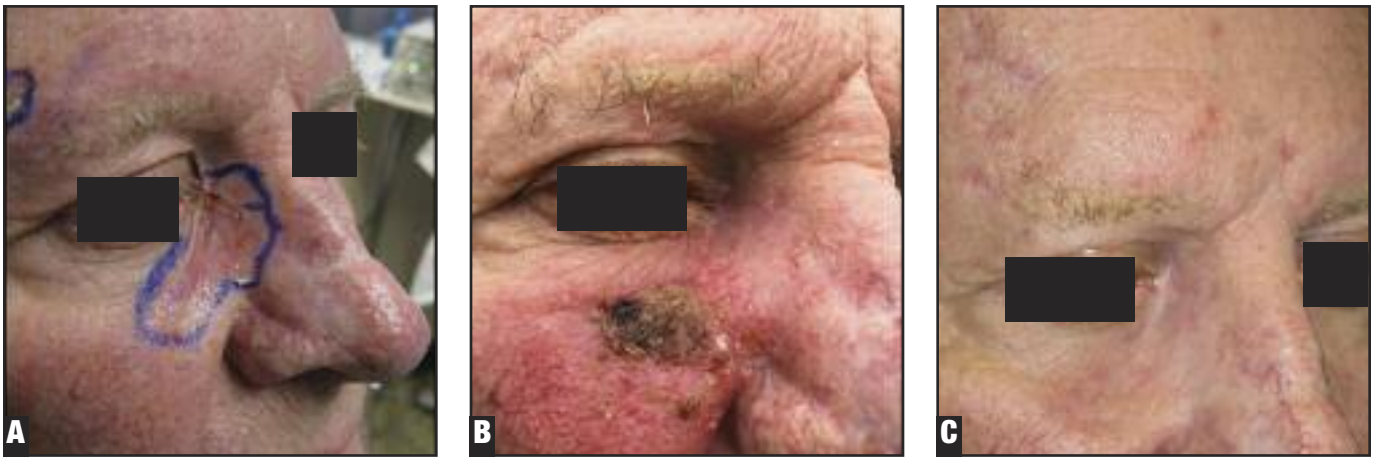

Figures 1A–1C. Clinical photos of a patient with basal cell carcinoma receiving the triple hedgehog pathway inhibition therapy. (A) Basal cell carcinoma around the right lower eyelid and medial canthus pretreatment. (B) Crusting of the lower eyelid and right cheek after two weeks of daily topical imiquimod. (C) Complete resolution at four weeks of the combined hedgehog inhibition

pathway has the potential of providing a higher rate of tumor regression compared to a single blocker for the treatment of advanced BCC, while limiting or delaying the development of acquired Hh pathway resistance (Figure 2). Vismodegib is an oral Hh pathway inhibitor that works at a receptor site on smoothened (SMO), a critical Hh pathway component. It is United States Food and Drug Administration (FDA)-approved for the treatment of advanced and metastatic BCC. Similarly, itraconazole inhibits Hh pathway activation at the level of SMO, but at a receptor that is distinct from the receptor that binds vismodegib.[2] The Hh pathway blocking effect of itraconazole is dose-dependent and independent of its well-known antifungal activity.[2]

Imiquimod, a topical imidazoquinoline, has antitumor properties via toll-like receptor agonist activity that leads to synthesis and release of various cytokines.[3] Additionally, imiquimod has been shown to repress Hh signalling activity via adenosine receptor activation (ADORA/PKA). This is far removed downstream from SMO and is separate from the inhibition sites of vismodegib and itraconazole.[3] Imiquimod is FDA-approved for the treatment of superficial BCC on the trunk and extremities, excluding sensitive areas such as the face. The off-label use of topical 5% imiquimod on the face for ulcerative BCC has been shown to promote healing with minimal scarring.[4] Mindful of the common side effects of erythema, crusting, and scabbing, the authors delayed imiquimod therapy to ensure adherence with vismodegib and itraconazole if the patient could not tolerate the skin irritation.

The authors' patient received outstanding results with side effects comparable to vismodegib therapy alone. At four months, there was no clinical or histological evidence of the locally advanced BCC. This is much shorter than vismodegib monotherapy for locally advanced BCC, with a 7.6-month median duration of response and only 21 percent of complete recovery.[5,6] Compared to vismodegib, itraconazole is less effective in reducing Hh pathway expression.[7,8] Furthermore, its lack of response in vismodegib-resistant patients suggests that itraconazole may be more useful as an adjunct, as opposed to a second-line monotherapy.[7]

Since the side effects of each blocker utilized by the authors' patient are different and not additive, their use in combination may provide for increased and prolonged efficacy with a similar side effect profile. This additive inhibitory effect on Hh-dependent

tumor growth, including tumors with acquired resistance to SMO inhibitors, has been reported using a combination of itraconazole and arsenic trioxide in mice.[9]

While it is not possible to make generalizations from the treatment of a single patient, results seen with the authors' patient should encourage the treatment of more patients with combination therapy. Clinical trials or the treatment of a larger group of patients with combination Hh inhibition is recommended to investigate the efficacy, adverse events, and incidence of resistance.

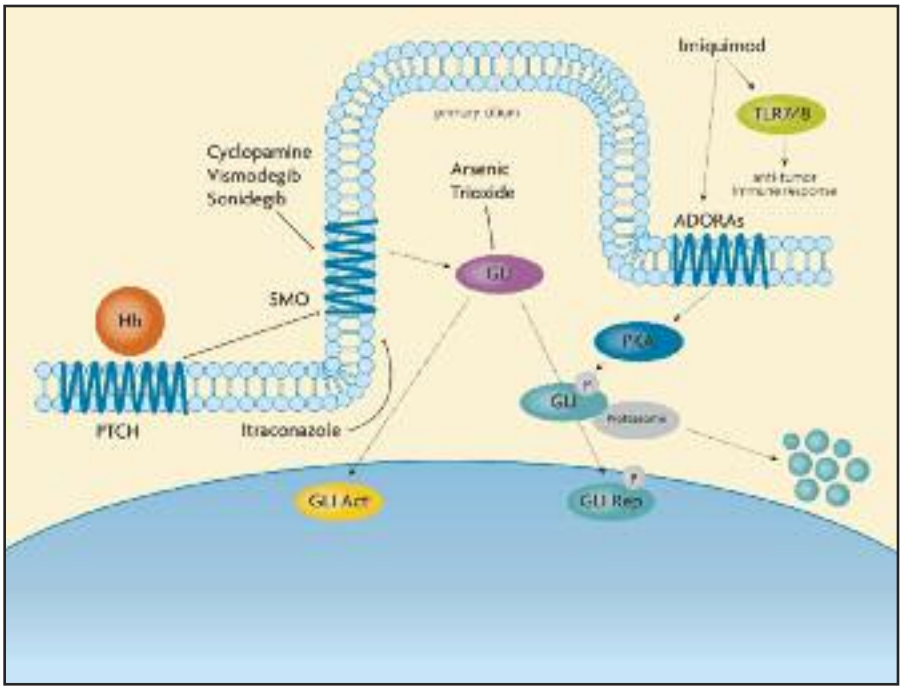

Figure 2. Mechanism of action of various Hedgehog pathway inhibitors. Both vismodegib and itraconazole antagonize Smoothened (SMO), but through independent pathways. Imiquimod stimulates adenosine receptor (ADORA), which activates the protein kinase A (PKA)-mediated phosphorylation (P) of the GLI transcription factors. This mechanism is autonomous from its action as a TLR7 and TLR8 agonist in the inflammatory pathway. Arsenic trioxide inhibits hedgehog signaling by directly inhibiting GLI transcriptional activity.

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